Design Issues in the Study of Rare Cancers

Rare Cancers Working Group Report

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Overview

- **Goal: solicit input from NCI investigators on the need to study rare cancers**
- **This workshop focused on adult tumors**
- **Childhood cancers were outside of our mandate since the majority (~ 90%) of children with cancer are already enrolled in clinical trials**

What is Rare?

- Incidence less than 15/100,000 cases

or

- Less than 40,000 cases per year in the US

Rare Cancers

	Annual Cases	Deaths	Death Rates
• Pancreas	31,860	31,270	98%
• Esophagus	14,250	13,300	93%
• Multiple myeloma	15,270	11,070	72%
• Leukemia	33,440	23,300	70%
• Brain	18,400	12,690	69%
• Ovary	25,580	16,090	63%
• Bones & joints	2,440	1,300	53%
• Soft tissue (including heart)	8,680	3,660	42%
• Uterine cervix	10,520	3,900	37%
• Kidney & renal pelvis	35,710	12,480	35%
• Ureter, other urinary organs	2,450	690	28%
• Vulva	3,970	850	21%
• Uterine corpus	40,320	7,090	18%
• Hodgkin's disease	7,880	1,320	17%
• Penis & other genital, male	1,570	270	17%
• Endocrine system	25,520	2,440	10%
• Thyroid	23,600	1,460	6%
• Testis	8,980	360	4%

– *ACS Estimates 2004*

Why Study Rare Cancers ?

- Some are highly lethal
- Some have rising rates (e.g. esophageal)
- May be informative about etiology of more common tumors
- Lower incidence tends to go with more heritability/familial (e.g. twin studies by N. Risch)
- Simpler etiology than common cancers
  - e.g. RB, angiosarcoma, clear cell carcinoma of vagina
  - May provide insight to more common and complex tumors
- Disproportionate in some ethnic groups (e.g. male breast cancer)
- YPLL from cancer at young age
- Total incidence of all rare cancers is substantial

Why Study Rare Tumors ?

- **Ethical Issues**
  - **Etiologic studies of rare tumors have been given less attention by the scientific community compared to more common cancers**
  - **Rare tumors deserve to receive their share of research**
  - **Patients afflicted with such cancers should not have to carry the burden of disease alone**
  - **Sense of hope in the search for a cure**

Rationale for First Study of a Rare Tumor

- **Compare with study # 101 of a common tumor**
- **Higher probability of a “hit”**

How to Study the Etiology of Rare Cancers?

- **Gather data**
  - **Descriptive data from SEER**
  - **Existing cohorts**
    - **With and without biospecimens**
    - **Number of cases**
    - **Questionnaire data available?**
    - **Biospecimen availability?**
  - **Existing clinical trials of rare tumors**

Study Design Options

- **Cohort Studies**
  - **Value: studies of modest size - using multiple existing cohorts**
  - **Should be able to identify moderate to strong risk factors**
    - **Questionnaire based analyses**
    - **Biologic samples**
  - **How to obtain access to questionnaire data and biologic samples?**

Study Design Options

- **Clinical Trials**
  - **Feasibility of adding etiology to treatment trials of rare diseases**
    - **Precedent: Childhood cancer**
  - **Methodologic issues**
    - **Bias: e.g. cases in clinical trials may have worst prognosis**
    - **Yes, but …**
    - **We cannot afford to be overly fastidious**
    - **Strong apparent risk factors are robust to small biases**

Study Design Options

- ***De novo* Designs**
  - **Why?**
    - **Follow-up hypotheses from cohort mining**
    - **Functional assays/phenotypes from samples, fresh tissue**
    - **Subgroups with molecular categorization**
    - **Integrate with studies of prognosis and treatment**

Basic Design

- Study multiple kinds of rare tumors
- Hospital based
  - At major cancer centers
  - “that’s where the money is”
- Common hospital or clinic controls
- Single questionnaire, biospecimen collection protocol
- Methodological challenges
  - Control selection
  - Surmountable

Building Infrastructure

- **Building Partnerships**
- **Take advantage of GCRCs**
- **Supplemental funds to Cancer Centers to explore feasibility**

General Suggestions

- **Create common rare tumor protocol**
- **Collect baseline information on all rare cancers (e.g. pooling, data sharing)**
- **Banking samples**
- **Studies comparing higher rates in populations**